CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number : 074579

Trade Name : BETAMETHASONE DIPROPIONATE CREAM USP 0.05% (BASE)

Generic Name: Betamethasone Dipropionate Cream USP 0.05% (base)

Sponsor : Clay-Park Labs, Inc.

Approval Date: November 26, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 074579

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	Included	Pending Completion	Not Prepared	Not Required
Approval Letter	X			
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Medical Review(s)				
Chemistry Review(s)	X			
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Pharmacology Review(s)				
Statistical Review(s)				
Microbiology Review(s)				
Clinical Pharmacology Biopharmaceutics Review(s)				
Bioequivalence Review(s)	X			
Administrative Document(s)				
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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 074579

APPROVAL LETTER

ANDA 74-579

NOV 26 1997

Clay-Park Labs, Inc.
Attention: Gabriel Lebovic
1700 Bathgate Avenue
Bronx, NY 10457

Dear Sir:

This is in reference to your abbreviated new drug application dated December 1, 1994, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Betamethasone Dipropionate Cream USP, 0.05% (base).

Reference is also made to your amendments dated September 12 and October 17, 1997.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Betamethasone Dipropionate Cream USP, 0.05% (base) to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Diprosone Cream, 0.05% of Schering Corporation).

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours.

11-26-97

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074579

FINAL PRINTED LABELING

NDC 45802-019-42

BETAMETHASONE DIPROPIONATE CREAM USP, 0.05%

(Potency expressed as betamethasone)

Each gram contains: 0.64 mg betamethasone dipropionate, USP (equivalent to 0.5 mg of betamethasone), in a hydrophilic emollient cream consisting of purified water, mineral oil, white petrolatum, polyethylene glycol 1000 cetyl ether, cetyl alcohol, stearyl alcohol, phosphoric acid, and monobasic sodium phosphate; propylene glycol and chlorocresol as preservatives.

Usual Dose: Apply a thin film of cream to the affected skin areas once a day. In some cases a twice daily dosage may be necessary.

Net Wt. 45 grams

For dermatological use only
Caution: Federal law prohibits dispensing without prescription.
Read accompanying directions carefully.
Store between 2° and 30° C (36° and 86° F).
Lot No. & Exp. Date: See crimp of tube or see box. R1
Mfg. By: Clay-Park Labs, Inc. Bronx, NY 10457

NDC 45802-019-42

BETAMETHASONE DIPROPIONATE CREAM USP, 0.05%

(Potency expressed as betamethasone)

Each gram contains: 0.64 mg betamethasone dipropionate, USP (equivalent to 0.5 mg of betamethasone), in a hydrophilic emollient cream consisting of purified water, mineral oil, white petrolatum, polyethylene glycol 1000 cetyl ether, cetyl alcohol, stearyl alcohol, phosphoric acid, and monobasic sodium phosphate; propylene glycol and chlorocresol as preservatives.

Usual Dose: Apply a thin film of cream to the affected skin areas once a day. In some cases a twice daily dosage may be necessary.

Net Wt. 45 grams

For dermatological use only
Caution: Federal law prohibits dispensing without prescription.
Read accompanying directions carefully.
Store between 2° and 30° C (36° and 86° F).
Lot No. & Exp. Date: See crimp of tube or see box. R1
Mfg. By: Clay-Park Labs, Inc. Bronx, NY 10457

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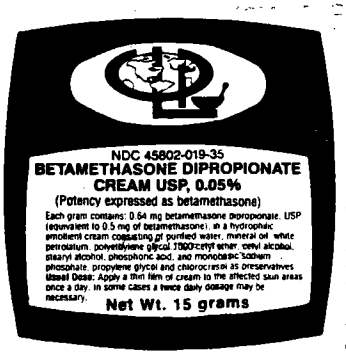
Mfg. By: Clay-Park Labs, Inc. Bronx, NY 10457

Margo



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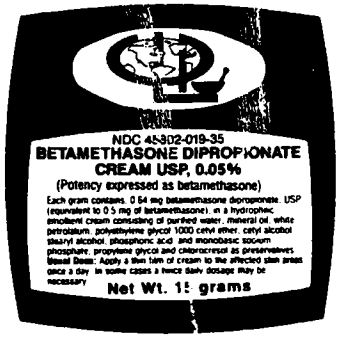
Mfg. By: Clay-Park Labs, Inc. Bronx, NY 10457



For dermatological use only
Caution: Federal law prohibits dispensing without prescription.
Read accompanying directions carefully.
Store between 2° and 30° C (36° and 86° F).
Lot No. & Exp. Date: See crimp of tube or see box. R1
Mfg. By: Clay-Park Labs, Inc. Bronx, NY 10457

CYAN BLK GREEN

Date:

01915CPL

Each gram contains: 0.64 mg betamethasone dipropionate, USP (equivalent to 0.5 mg of betamethasone) a hydrophilic, emollient cream consisting of purified water, mineral oil, white petrolatum, polyethylene glycol 1000 cetyl ether, cetyl alcohol, stearyl alcohol, phosphoric acid, and monobasic sodium phosphate; propylene glycol and chlorocresol as preservatives.
Usual Dose: Apply a thin film of cream to the affected skin areas once a day. In some cases a twice daily dosage may be necessary.

BDN

NDC 45802-019-35

BETAMETHASONE DIPROPIONATE CREAM USP, 0.5%

(Potency expressed as betamethasone)

NET WT. 15 g

APPROVED

For dermatological use only
Caution: Federal law prohibits dispensing without prescription.
Read accompanying directions carefully.
Store between 2° and 30° C (36° and 86° F).
Lot No. & Exp. Date: See crimp of tube or see box. R1
Mfg. By: Clay-Park Labs, Inc. Bronx, NY 10457

R0795

0 81642 01935 3

NDC 45802-019-35

BETAMETHASONE DIPROPIONATE CREAM USP, 0.5%

(Potency expressed as betamethasone)

NET WT. 15 g

APPROVED

R0795

Each gram contains: 0.64 mg betamethasone dipropionate, USP (equivalent to 0.5 mg of betamethasone) a hydrophilic, emollient cream consisting of purified water, mineral oil, white petrolatum, polyethylene glycol 1000 cetyl ether, cetyl alcohol, stearyl alcohol, phosphoric acid, and monobasic sodium phosphate; propylene glycol and chlorocresol as preservatives. **Usual Dose:** Apply a thin film of cream to the affected skin areas once a day. In some cases a twice daily dosage may be necessary.

01945CPL

NDC 45802-019-42

BETAMETHASONE DIPROPIONATE CREAM USP, 0.5%

(Potency expressed as betamethasone)

NET WT. 45 g

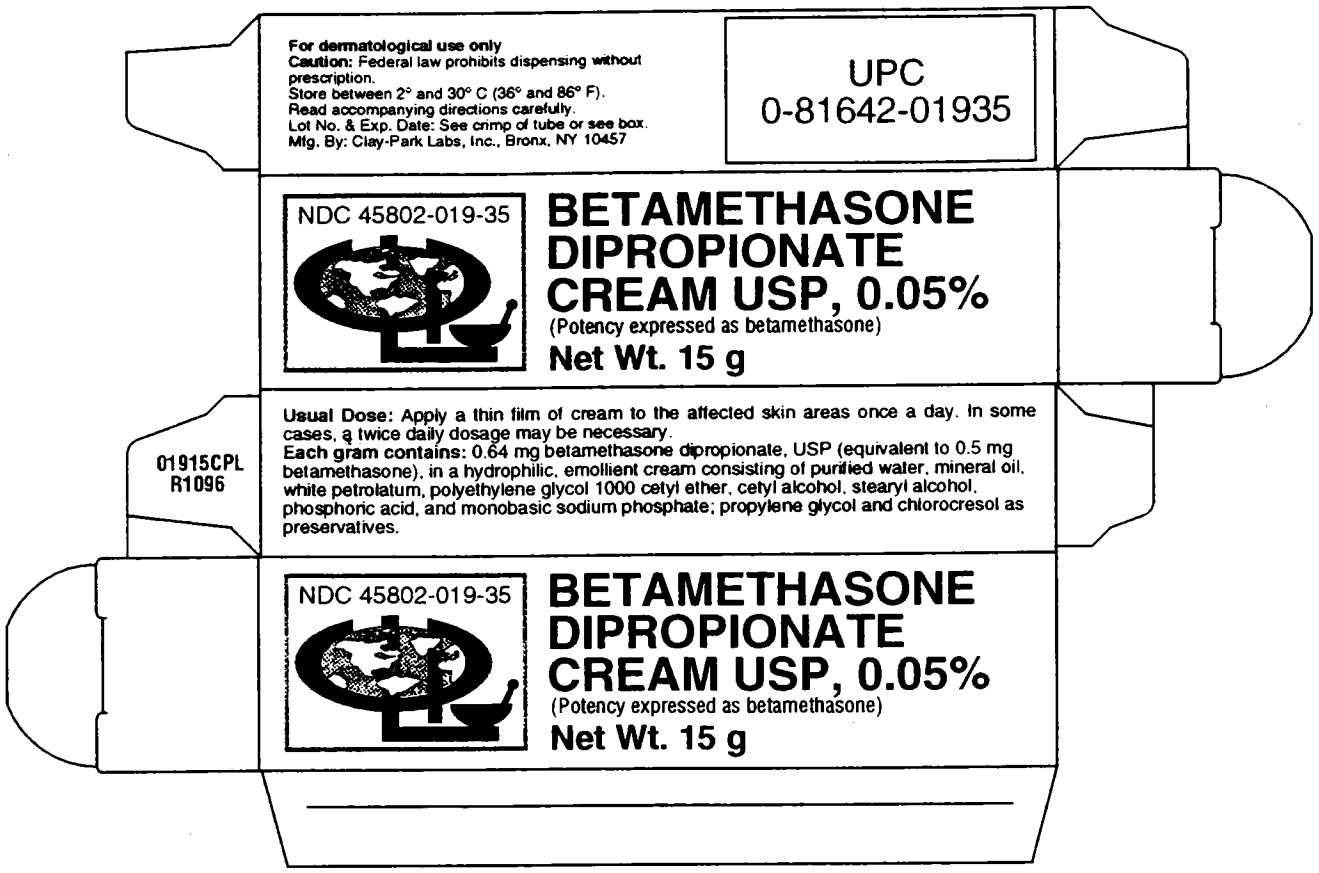
For dermatological use only
Caution: Federal law prohibits dispensing without prescription.
Read accompanying directions carefully.
Store between 2° and 30° C (36° and 86° F).
Lot No. & Exp. Date: See crimp of tube or see box. R1
Mfg. By: Clay-Park Labs, Inc. Bronx, NY 10457

0 81642 01942 1

NDC 45802-019-42

BETAMETHASONE DIPROPIONATE CREAM USP, 0.5%

(Potency expressed as betamethasone) NET WT. 45 g



DIE # C8061

CODE # 108

PMS 320, BLACK

For dermatological use only
Caution: Federal law prohibits dispensing without prescription.
Store between 2° and 30° C (36° and 86° F).
Read accompanying directions carefully.
Lot No. & Exp. Date: See crimp of tube or see box.
Mfg. By: Clay-Park Labs, Inc., Bronx, NY 10457

UPC
0-81642-01942

NDC 45802-019-42

BETAMETHASONE DIPROPIONATE CREAM USP, 0.05%

(Potency expressed as betamethasone)

Net Wt. 45 g

Usual Dose: Apply a thin film of cream to the affected skin areas once a day. In some cases, a twice daily dosage may be necessary.
Each gram contains: 0.64 mg betamethasone dipropionate, USP (equivalent to 0.5 mg betamethasone), in a hydrophilic, emollient cream consisting of purified water, mineral oil, white petrolatum, polyethylene glycol 1000 cetyl ether, cetyl alcohol, stearyl alcohol, phosphoric acid, and monobasic sodium phosphate; propylene glycol and chlorocresol as preservatives.

01945CPL
R1096

NDC 45802-019-42

BETAMETHASONE DIPROPIONATE CREAM USP, 0.05%

(Potency expressed as betamethasone)

Net Wt. 45 g

DIE # C7062G CODE # 108 PMS 320, BLACK

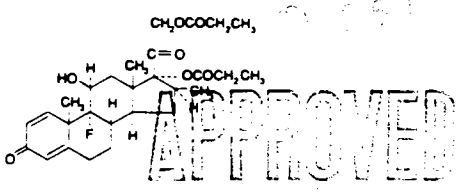
BETAMETHASONE DIPROPIONATE

Cream, USP 0.05%
Lotion, USP 0.05% w/w
(Potency Expressed as Betamethasone)
For Dermatologic Use Only - Not for Ophthalmic Use

DESCRIPTION

Betamethasone Dipropionate products contain betamethasone dipropionate, USP, a synthetic adrenocorticosteroid, for dermatologic use. Betamethasone, an analog of prednisolone, has high corticosteroid activity and slight mineralocorticoid activity. Betamethasone dipropionate is the 17, 21-dipropionate ester of betamethasone.

Chemically, betamethasone dipropionate is 9-Fluoro-11β,17, 21-trihydroxy-16β-methyl-pregna-1,4-diene-3, 20-dione 17, 21-dipropionate, with the molecular formula $C_{28}H_{37}FO_7$, a molecular weight of 504.6, and the following structural formula:



Betamethasone dipropionate is a white to creamy white, odorless crystalline powder, insoluble in water.

Each gram of Betamethasone Dipropionate Cream 0.05% contains: 0.64 mg betamethasone dipropionate, USP (equivalent to 0.5 mg betamethasone), in a hydrophilic emollient cream consisting of purified water, mineral oil, white petrolatum, polyethylene glycol 1000 cetyl ether, cetyl alcohol, stearyl alcohol, phosphoric acid, and monobasic sodium phosphate; propylene glycol and chlorocresol as preservatives.

Each gram of Betamethasone Dipropionate Lotion 0.05% w/w contains: 0.64 mg betamethasone dipropionate, USP (equivalent to 0.5 mg betamethasone), in a lotion base of diisopropyl adipate (46.8%) and purified water slightly thickened with carbopol 934-P; the pH is adjusted to approximately 4.7 with sodium hydroxide.

CLINICAL PHARMACOLOGY

The corticosteroids are a class of compounds comprising steroid hormones secreted by the adrenal cortex and their synthetic analogs. In pharmacologic doses corticosteroids are used primarily for their anti-inflammatory and/or immunosuppressive effects.

Topical corticosteroids, such as betamethasone dipropionate, are effective in the treatment of corticosteroid-responsive dermatoses primarily because of their anti-inflammatory, antipruritic, and vasoconstrictive actions. However, while the physiologic, pharmacologic, and clinical effects of the corticosteroids are well-known, the exact mechanisms of their actions in each disease are uncertain. Betamethasone dipropionate, a corticosteroid, has been shown to have topical (dermatologic) and systemic pharmacologic and metabolic effects characteristic of this class of drugs.

Pharmacokinetics

The extent of percutaneous absorption of topical corticosteroids is determined by many factors including the vehicle, the integrity of the epidermal barrier, and the use of occlusive dressings. (See **DOSAGE AND ADMINISTRATION** section.)

Topical corticosteroids can be absorbed from normal intact skin. Inflammation and/or other disease processes in the skin increase percutaneous absorption. Occlusive dressings substantially increase the percutaneous absorption of topical corticosteroids. (See DOSAGE AND ADMINISTRATION section.)

Once absorbed through the skin, topical corticosteroids are handled through pharmacokinetic pathways similar to systemically administered corticosteroids. Corticosteroids are bound to plasma proteins in varying degrees. Corticosteroids are metabolized primarily in the liver and are then excreted by the kidneys. Some of the topical corticosteroids and their metabolites are also excreted into the bile.

INDICATIONS AND USAGE

Betamethasone Dipropionate products are indicated for relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses.

CONTRAINDICATIONS

Betamethasone Dipropionate products are contraindicated in patients who are hypersensitive to betamethasone dipropionate, to other corticosteroids or to any ingredient in these preparations.

PRECAUTIONS

General: Systemic absorption of topical corticosteroids has produced reversible hypothalamic-pituitary-adrenal (HPA) axis suppression, manifestations of Cushing's syndrome, hyperglycemia, and glucosuria in some patients.

Conditions which augment systemic absorption include the application of the more potent steroids, use over large surface areas, prolonged use, and the addition of occlusive dressings. (See **DOSAGE AND ADMINISTRATION** section.)

Therefore, patients receiving a large dose of a potent topical steroid applied to a large surface area should be evaluated periodically for evidence of HPA axis suppression by using the urinary free cortisol and ACTH stimulation tests. If HPA axis suppression is noted, an attempt should be made to withdraw the drug, to reduce the frequency of application, or to substitute a less potent steroid.

Recovery of HPA axis function is generally prompt and complete upon discontinuation of the drug. Infrequently, signs and symptoms of steroid withdrawal may occur, requiring supplemental systemic corticosteroids.

Children may absorb proportionally larger amounts of topical corticosteroids and thus be more susceptible to systemic toxicity. (See **PRECAUTIONS-Pediatric Use.**)

If irritation develops, topical corticosteroids should be discontinued and appropriate therapy instituted.

In the presence of dermatological infections, the use of an appropriate antifungal or antibacterial agent should be instituted. If a favorable response does not occur promptly, the corticosteroid should be discontinued until the infection has been adequately controlled.

Information for Patients

Patients using topical corticosteroids should receive the following information and instructions:

1. This medication is to be used as directed by the physician. It is for external use only. Avoid contact with the eyes.
2. Patients should be advised not to use this medication for any disorder other than for which it was prescribed.
3. The treated skin area should not be bandaged or otherwise covered or wrapped as to be occlusive. (See **DOSAGE AND ADMINISTRATION** section.)
4. Patients should report any signs of local adverse reactions.
5. Parents of pediatric patients should be advised not to use tight-fitting diapers or plastic pants on a child being treated in the diaper area, as these garments may constitute occlusive dressing. (See **DOSAGE AND ADMINISTRATION** section.)

Laboratory Tests

The following tests may be helpful in evaluating HPA axis suppression:

Urinary free cortisol test

ACTH stimulation test

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Long-term animal studies have not been performed to evaluate the carcinogenic potential or the effect on fertility of topical corticosteroids.

Studies to determine mutagenicity with prednisolone have revealed negative results.

Pregnancy: Teratogenic Effects

Pregnancy Category C: Corticosteroids are generally teratogenic in laboratory animals when administered systemically at relatively low dosage levels. The more potent corticosteroids have been shown to be teratogenic after dermal application in laboratory animals. There are no adequate and well-controlled studies in pregnant women on teratogenic effects from topically applied corticosteroids. Therefore, topical corticosteroids should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Drugs of this class should not be used extensively on pregnant patients, in large amounts, or for prolonged periods of time.

Nursing Mothers

It is not known whether topical administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in breast milk. Systemically administered corticosteroids are secreted into breast milk in quantities not likely to have a deleterious effect on the infant. Nevertheless, caution should be exercised when topical corticosteroids are prescribed for a nursing woman.

Pediatric Use

Pediatric patients may demonstrate greater susceptibility to topical corticosteroid-induced HPA axis suppression and Cushing's syndrome than mature patients because of a greater skin surface area to body weight ratio.

Hypothalamic-pituitary-adrenal (HPA) axis suppression, Cushing's syndrome, and intracranial hypertension have been reported in children receiving topical corticosteroids. Manifestations of adrenal suppression in children include linear growth retardation, delayed weight gain, low plasma cortisol levels, and absence of response to ACTH stimulation. Manifestations of intracranial hypertension include bulging fontanelles, headaches, and bilateral papilledema.

Administration of topical corticosteroids to children should be limited to the least amount compatible with an effective therapeutic regimen. Chronic corticosteroid therapy may interfere with the growth and development of children.

ADVERSE REACTIONS

The following local adverse reactions are reported infrequently when Betamethasone Dipropionate products are used as recommended in the **DOSAGE AND ADMINISTRATION** section. These reactions are listed in an approximate decreasing order of occurrence: burning; itching; irritation; dryness; folliculitis; hypertrichosis; acneiform eruptions; hypopigmentation; perioral dermatitis; allergic contact dermatitis; maceration of the skin; secondary infection; skin atrophy; striae; miliaria.

Systemic absorption of topical corticosteroids has produced reversible hypothalamic-pituitary-adrenal (HPA) axis suppression, manifestations of Cushing's syndrome, hyperglycemia, and glucosuria in some patients.

OVERDOSAGE

Topically applied corticosteroids can be absorbed in sufficient amounts to produce systemic effects. (See **PRECAUTIONS.**)

DOSAGE AND ADMINISTRATION

Betamethasone Dipropionate cream: Apply a thin film of Betamethasone Dipropionate Cream 0.05% to the affected skin areas once daily. In some cases, a twice daily dosage may be necessary.

Betamethasone Dipropionate lotion: Apply a few drops Betamethasone Dipropionate lotion 0.05% to the affected area; massage lightly until it disappears. Apply twice daily, in the morning and at night. For the most effective and economical use, apply nozzle very close to affected area and gently squeeze bottle.

HOW SUPPLIED

Betamethasone Dipropionate Cream 0.05% is supplied in 15 gram (NDC 45802-019-35) and 45 gram (NDC 45802-019-35) tubes; boxes of one.

Betamethasone Dipropionate Lotion 0.05% w/w is available in 20 mL (NDC 45802-021-97) and 60 mL (NDC 45802-021-46) plastic squeeze bottles; boxes of one.

Protect from light. Store in cartons until contents are used.

Store all BETAMETHASONE DIPROPIONATE preparations between 2° and 30° C (36° and 86° F).

Clay-Park Labs, Inc.
Bronx, NY 10457

Mfg. by: Clay-Park Labs, Inc., Bronx, NY 10457

Rev. 1-95

APPROVED

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074579

CHEMISTRY REVIEW(S)

1. CHEMISTRY REVIEW NO. 4

2. ANDA # 74-579

3. NAME AND ADDRESS OF APPLICANT

Clay-Park Labs, Inc.
Attention: Mr. Gabriel Lebovic
1700 Bathgate Avenue
Bronx, NY 10457

4. BASIS OF SUBMISSION
The ANDA is based on the approved listed drug, Diprosone Cream 0.05%, the subject of NDA 17-536, held by Schering Corporation. There is no remaining patent or marketing exclusivity for Diprosone Cream 0.05%.

5. SUPPLEMENT(s) N/A 8. SUPPLEMENT(s) PROVIDE(s) FOR: N/A

6. PROPRIETARY NAME
None.

7. NONPROPRIETARY NAME
Betamethasone Dipropionate Cream USP, 0.05%

9. AMENDMENTS AND OTHER DATES:

12/01/94 Original ANDA.
04/20/95 NA letter.

10/11/95 Minor amendment (chemistry and labeling).
10/24/95 Telecon from Angela Payne to firm.
11/12/95 Final printed inserts.
01/25/96 NA letter - chemistry only.

10/29/96 Chemistry minor amendment.
11/01/96 Gratuitous labeling telephone amendment - corrected color printed carton labeling.
11/20/96 **First telecon** requesting chemistry information.
11/21/96 Minor chemistry amendment responding to telecon of 11/20/96.
12/06/96 **Second telecon** requesting chemistry information.
12/12/96 Minor chemistry amendment responding to telecon of 12/06/96.
12/17/96 **Third telecon** requesting chemistry information.
12/18/96 Minor chemistry amendment responding to telecon of 12/17/96.
01/09/97 **Fourth telecon** requesting chemistry information.
01/10/97 Minor chemistry amendment responding to telecon of 01/09/97.

01/14/97 **Fifth telecon** requesting chemistry information.
01/15/97 Minor chemistry amendment responding to telecon of 01/14/97.
01/17/97 **Sixth telecon** requesting chemistry information.
01/17/97 Minor chemistry amendment responding to telecon of 01/17/97. **This amendment contained a commitment to submit impurities limits for the DS and DP as a CBE supplement before marketing the product.**
05/20/97 NA-Minor letter for GMP problems.

09/12/97 N/AA amendment: APET results were submitted as a follow-up to Clay-Park's letter to FDA dated 12/18/96. The results are acceptable.
10/17/97 Minor amendment in response to NA letter of 5/20/97. GMP problems have been remedied.
11/10/97 Minor telephone amendment - commitment to make viscosity a part of the release and stability specs.

10. PHARMACOLOGICAL CATEGORY

A synthetic adrenocorticosteroid for dermatologic use. Indicated for the relief of the inflammatory and pruritic manifestations of corticosteroid responsive dermatoses.

11. Rx or OTC Rx

12. RELATED IND/NDA/DMF(s)

13. DOSAGE FORM Cream 14. STRENGTH 0.05%

15. CHEMICAL NAME AND STRUCTURE

$C_{28}H_{37}FO_7$ 504.59 *CAS-5593-20-4*

Pregna-1,4-diene-3,20-dione, 9-fluoro-11-hydroxy-16-methyl-17,21-bis(1-oxopropoxy)-,(11β,16β)

9-Fluoro-11β,17,21-trihydroxy-16β-methylpregna-1,4-diene-3,20-dione 17,21-dipropionate

16. RECORDS AND REPORTS N/A

17. COMMENTS

All CMC deficiencies have been resolved.

The following Points have been completed and are satisfactory:

31. Samples and Results
32. Labeling
33. Establishment Inspection
34. Bioequivalence Status

18. CONCLUSIONS AND RECOMMENDATIONS

ANDA 74-579 CAN BE APPROVED.

19. REVIEWER:	DATE COMPLETED:	DATE REVISED:
Eugene L. Schaefer, Ph.D.	11/7/97	11/17/97

Endorsed by P.Schwartz, Ph.D.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074579

BIOEQUIVALENCE REVIEW(S)

OFFICE OF GENERIC DRUGS, HFD640

Microbiologists Review #1

November 5, 1997

A. 1. ANDA: **74-579**

APPLICANT: Clay-Park Labs, Inc.
Attention: Giabriel Lebovic
1700 Bathgate ave.
Bronx, NY 10457

2. PRODUCT NAME: **Betamethasone Dipropionate Cream, 0.05%, USP**
3. DOSAGE FORM AND ROUTE OF ADMINISTRATION:
4. METHOD(S) OF STERILIZATION: Aseptic filling.
5. PHARMACOLOGICAL CATEGORY: synthetic corticosteroid

B. 1. DATE OF INITIAL SUBMISSION:
2. DATE OF AMENDMENT: **September 12, 1997.- Subject of this review.**
3. RELATED DOCUMENTS:
4. ASSIGNED FOR REVIEW: November 5, 1997.

C. REMARKS: Review of Antimicrobial Preservative Effectiveness testing at 0%, 50%, 80% and 100% preservative concentrations.

D. CONCLUSIONS: The submission is are recommended for approval on the basis of antimicrobial preservative activity.

11/6/97
James L. McVey

initialed by R. Patel RPatel 11/6/97

cc:

Original ANDA
Duplicate ANDA
Field Copy
drafted by: J. McVey 74579ap1.m

FEB 6 1996

Betamethasone Dipropionate
0.05% Cream
ANDA # 74-579
Reviewer: Andre J. Jackson
WP #74579S.D94

Clay Park Laboratories
Bronx, New York
Submission Dated:
December 1, 1994

REVIEW OF TOPICAL CORTICOSTEROID BIOEQUIVALENCE STUDY

Background

In July of 1992, the Division of Bioequivalence issued an interim guidance "Topical Corticosteroids: In vivo Bioequivalence and in Vitro Release Methods". This document outlined the agency's proposed bioequivalence study design. The design involved 36 healthy subjects receiving 10 ul of generic test formulation applied to circular, 2-cm diameter sites on one arm and reference formulation applied to sites on the contralateral arm. The sites were to be evaluated by both a chromameter and visually at 0.25, 0.5, 1, 2, 4, 8, 10 and 24 hours after removal of the formulation. In addition, a sixteen hour duration of application, with reading two hours after removal of formulation, was to be included. Following a washout, the study was to be repeated in the same subjects, using a second lot of the reference product and same test lot. Data analysis was to consist of fitting dose\response curves (Emax model) to the area under the response curves and maximum responses for the test and reference treatments in each subject.

On June 2, 1995, the Division of Bioequivalence issued a new guidance for the conduct of studies for topical corticosteroids which supercedes the July 1992 guidance. The current guidance is based upon the conduct of two studies by the firm- a pilot dose duration-response study and a pivotal in vivo bioequivalence study comparing test and reference products.

The current study did not meet the criteria related to evaluation by the E-max model per the 1992 guidance and it was completed and submitted prior to the issue of the 1995 guidance. Therefore, the study was evaluated via consult by David C. Bostwick, HFD-630.

Objective:

The aim of this study is to compare the relative vasoconstrictive effects of corresponding test and reference betamethasone topical cream formulations in asymptomatic subjects, and using the generic as a negative control The reference product is 0.05%

Diprosone cream manufactured by Schering Corporation.

Methods:

The study was conducted by under the direction of The study was done on the following dates: Period I, Group I-8-3-93
Period I, Group II-8-10-93
Period II, Group I-8-24-93
Period II, Group II-8-31-93

I. Characterization of Study Group:

A. Inclusion criteria

1. All volunteers selected for this study were female volunteers between the ages of 18 and 48 years. Weight range of the volunteers was within 30% of normal body weight relative to height and frame size as described in the "Table of Desirable Weights of Adults" published by the Metropolitan Life Insurance Company in 1983.

2. Good health, as determined by evaluation of a medical history prior to study initiation. Female subjects, who are not post-menopausal or surgically sterilized, will be tested for pregnancy prior to study initiation with blood or urine pregnancy test.

3. Known vasoconstrictor response to topical corticosteroids.

B. Exclusion Criteria:

1. History of allergy to betamethasone, to any corticosteroids, or to any creams, lotions, ointments, or cosmetics.

2. Volunteers with a history of alcohol or drug abuse.

3. History of serious gastrointestinal, renal, hepatic, cardiovascular or hematological diseases.

4. Any skin condition or coloration which would interfere with assessment of skin blanching.

5. Participation in a previous clinical trial within 28 days of dosing.

6. Use of any OTC medication on a regular basis.

7. Use of any systemic or topical corticosteroid within 30 days of dosing.

8. Pregnancy of any female subject at the time of the study.

Restrictions

1. Subjects were instructed to take no prescribed or OTC medication for at least 14 days prior to the initial dosing and throughout the study.

2. The subjects had to avoid contact with water on their arms, extremes of temperature and vigorous exercise during the study.

C. Informed Consent:
All prospective volunteers had the study explained by a member of the research team or a member of their staff. The nature of the drug substance to be evaluated was explained together with the potential hazards involving drug allergies and possible adverse reactions. An acknowledgement of the receipt of this information and the participant's freely-tendered offer to volunteer was obtained in writing from each participant in the study.

II. Study Conduct

The study was done in 40, healthy caucasian females.

A. Subjects were assigned to one of two treatment groups(See attached randomization scheme.) The locations of the test and reference creams were determined by random assignment. Seven circular application sites were designated on the flexor surface of the forearm between the wrist and the elbow. After baseline chromameter readings, an open washer was positioned over each site and taped to the forearm. The location of treated and untreated sites were done by random assignment. A 10 ul application of the test and the reference creams was applied, using a 250 ul glass Hamilton syringe, to the remaining 5 sites on each arm.

At 0.5, 1,2,6 and 16 hours after application, one washer was removed from both a test and reference site and the residual surface cream was removed by gently wiping three times with a tissue. The washers at the untreated and vehicle sites were removed 6 hours after application and the sites were similarly wiped. Chromameter and visual assessments of the

blanching response at each site were made at 6, 8, 10, 12, 15, 18 and 24 hours post-application. After a 3-week washout, the same study procedures were followed except a second reference lot was applied to the opposite arm.

B. The products employed in the study were:

1. Test: 10 ul betamethasone dipropionate 0.05% cream, Lot # CPL P725.

2. Reference product: 10 ul Diprosone^{R} 0.05% cream
Schering Corporation Lot # KGD 303(Period I)
Schering Corporation Lot # KGD 102(Period II)

There was a 3 week washout between doses.

C. The randomization scheme is presented in attachment 1.

The formulation for the test prduct is given in attachment 2.

Results:

The data from the study was analyzed by Dave Bostwick HFD-630. Results from the consult are appended to this review.

Recommendation:

1. The bioequivalence study conducted by Clay Park Laboratories on its betamethasone dipropionate 0.05% cream Lot No. CPL P 725, comparing it to Schering's Diprosone cream 0.05% Lot Numbers KGD 303 and KGD 102 has been found to be acceptable by the Division of Bioequivalence. Therefore, betamethasone dipropionate 0.05% cream manufactured by Clay Park Laboratories should be deemed bioequivalent to Diprosone cream 0.05% manufactured by Schering.

BETAMETHASONE DIPROPIONATE .05% CREAM
STUDY NO. 9316902C

PERIOD 1
TREATMENT ASSIGNMENTS

SUBJ	LEFT ARM			RIGHT ARM		
	TREAT-MENT	VEHICLE POSITION	UNTREATED POSITION	TREAT-MENT	VEHICLE POSITIO"	UNTREATED POSITIO
1			7			
2			2			
3			1			
4			3			
5			2			
6			5			
7			4			
8			4			
9			5			
10			7			
11			6			
12			4			
13			6			
14			5			
15			6			
16			5			
17			3			
18			1			
[illegible]			5			
[illegible]			2			
21			7			
22			6			
23			3			
24			3			
25			7			
26			3			
27			3			
28			5			
29			5			
30			6			
31			6			
32			1			
33			2			
34			2			
35			6			
36			6			
37			7			
38			3			
39			3			
40			4			

BETAMETHASONE DIPROPIONATE
STUDY NO. 9316902C

TABLE C3: SUMMARY OF ADVERSE EVENTS

Duration:
Onset-End
H = Hours
D = Days
(If >24 Hours)

Severity (Sev):
1 = Mild
2 = Moderate
3 = Severe

Action Taken (Act):
1 = None
2 = Subject discontinued
3 = Other (see CRF)

Relationship (Rel):
1 = None
2 = Remote
3 = Possible
4 = Probable

Outcome (Out):
1 = Recovered
2 = AE continuing
3 = Subject lost to follow-up
4 = Other (see CRF)

Sub	Adverse Event	Onset (Per/Day)	Duration (Times)	Sev	Act	Rel	Out
01	Stuffy nose	I/14	0200-(29 H)	1	3	1	1
02	Headache	I/*	0600-1130	1	3	1	1
03	Multiple environmental allergies	I/18	1400-(53 H)	1	3	1	1
07	Headache	I/14	0200-(31 H)	1	3	1	1
09	Headache	I/19	1000-1100	2	3	1	1
14	Headache	I/19	0900-1000	1	3	1	1
15	Constipation	I/19	1200-(28 H)	1	3	1	1
	Headache	II/1	0330-1315	1	3	1	1
17	Cold symptoms	I/20	2030-(3 D)	1	3	1	1
20	Yeast infection	I/17	1400-(6 D)	2	3	1	1
26	Emesis x 3	II/1	1930-2055	1	3	1	1
38	Headache	I/1	1130-2200	1	3	1	1

* Adverse event began 2 hours prior to dosing in Period II.

Date of Review: June 19, 1995

Consultative Review of Vasoconstrictor Assay - NDA 74-579
(Referred by Division of Bioequivalence, HFD-650).

Sponsor: Clay - Park Laboratories
Bronx, N.Y. 10457

Product: Betamethasone Dipropionate Cream, , 0.05%

Purpose of Submission: To establish the equivalency of the Clay - Park product to the similar Diprosone Cream marketed by Schering.

Date of Submission: December 1, 1994.

Investigator:

Background: The vasoconstrictor assay has been used for some time as the test by which the relative potency of topical corticosteroid formulations is established. Because vasoconstrictor methodology was not standardized, and because questions have been raised about the ability of this methodology to detect differences in the potency of topical steroid products, the office of Generic Drugs (with consultation from this Division) has devised new methods to test the bioequivalency of topical steroids. An Interim Guidance for the performance of bioequivalence studies of topical steroids was issued on July 1, 1992. This application is the first which has been received which attempts to follows this guideline.

The Guidance was altered in late 1994. Since the study reviewed here was performed prior to issuance of the revised Guidance, the 1992 Guidance will be referred to in this document.

Formulations: The formulations of the Clay - Park and Schering products are similar.

Indication: These products are indicated for relief of the inflammatory and pruritic manifestations of corticosteroid - responsive dermatoses.

Method: This was a study of the relative vasoconstrictor effects of Clay - Park's 0.05% betamethasone dipropionate cream, the Clay - Park vehicle, and Schering's Diprosone Cream.

The following is an outline of the vasoconstrictor study proposed in the 1992 Guidance:

- 36 healthy subjects;
- Test formulation application to one arm; reference formulation to contralateral arm;
- 10 µl of single strength of product applied over a 2 cm diameter area with application area protected but unoccluded;
- Test and reference products removed after 0.25, 0.5, 1, 2 and 6 hours to provide five 'doses' (durations of application);
- Assessment of vasoconstrictor response at each site at 0.25, 0.5, 1, 2, 4, 6, 8, 10 and 24 hours, when applicable, after removal of the formulation;
- In addition, a sixteen hour duration of application, followed by a two hour reading post removal of the drug, should be included to correspond to pre-July 1992 requirements;
- Vasoconstrictor response assessed both visually and using the chromameter;
- Repeat study (replicate design) after suitable washout using second lot of reference product and switching arms for test and reference products;
- Application/measurement of suitable blanks (untreated skin and vehicle-only treatment skin) and calibrators to validate bioassay.

At each 'dose' (duration of application in the above example), the time course of response can yield the following variables: peak effect (E_{Peak}), time of this effect (T_{Peak}) and area under the effect/time curve from E_{0N} to the point at which the affect returns to E_0. Parameters describing the dose/response relationship (e.g., E_{Max}, EC_{50} and E_0) can be calculated for each subject and both test and reference formulations by fitting the peak response at each 'dose' to an appropriate pharmacodynamic model..

The following is an outline of the protocol performed by the test facility:

- 40 healthy female subjects
- Test formulation application to one arm; reference formulation to contralateral arm;
- 10 µl of test products applied over 1.6 cm diameter area with application area protected but unoccluded;

- Test and reference products removed after 0.5, 1, 2, 6 and 16 hours to provide five durations of application; (the test facility found that the 0.25 hour duration application did not provide a visually detectable blanching response);

- Assessment of vasoconstrictor response at each site at 6, 8, 10, 12, 15, 18 and 24 hours post-application; (the test facility found that the assessments prior to 6 hours post - application showed little if any blanching activity);

- Vasoconstrictor response assessed both visually and using the chromameter;

- After a 3 · week washout, the same study procedures were followed with a second lot of reference product applied to the opposite arm;

- The Clay - Park vehicle was used to validate the assay.

Visual scoring used the following scale:

0=No pallor; no change from surrounding area.
1=Mild pallor: slight or indistinct outline of application site.
2=Moderate pallor: discernable outline of application site.
3=Intense pallor: clean, distinct outline of application site.

Results:

A. Chromameter

The post - application chromameter readings were first adjusted by subtracting the baseline reading. The test facility notes that there was extreme intra - subject variability in chromameter response. This variability led to low statistical power and wide 90% conference intervals, especially for the shorter deadlines of application. This is illustrated by the following tables, taken from the sponsors submission (the "test" product is Clay - Park's , while the "reference" is Diprosone):

Comparison of Test and Reference corrected baseline-adjusted chromameter (a-scale) results for different durations of application in Period I.

Duration	Least Squares Means		Observed Diff. (%) *	90% Conf. Intervals (%)		
	Test	Reference		Power	Lower	Upper
Area						
0.5 hour	18.76	16.44	14.14	0.23	-12.8	41.0
1.0 hour	21.66	19.18	12.94	0.26	-11.7	37.6
2.0 hour	26.25	25.82	1.67	0.48	-15.6	19.0
6.0 hour	29.82	28.44	4.83	0.57	-10.5	20.2
Maximum						
0.5 hour	1.928	1.736	11.03	0.32	-10.8	32.9
1.0 hour	2.026	1.965	3.10	0.39	-16.3	22.5
2.0 hour	2.425	2.528	-4.06	0.61	-18.8	10.7
6.0 hour	2.685	2.706	-0.79	0.72	-13.7	12.1

Chromameter results for the 16- hour duration of application in Period I.

Reading	Least Squares Means		Observed Diff. (%)*	90% conf. Intervals (%)		
	Test	Reference		Power	Lower	Upper
18 hour	1.905	1.905	-0.01	0.39	-19.5	19.5

*None of the differences was detected as statistically significant by ANOVA (a = 0.05.)

Comparison of Test Reference corrected baseline-adjusted chromameter (a-scale) results for different durations of application in Period II.

	Least Squares Means		Observed Diff.	90% Conf. Intervals (%)		
Duration	Test	Reference	(%) *	Power	Lower	Upper
Area						
0.5 hour	16.73	15.90	5.18	0.18	-26.2	36.5
1.0 hour	18.09	17.46	3.65	0.37	-16.4	23.7
2.0 hour	22.11	20.52	7.75	0.44	-10.4	25.9
6.0 hour	23.72	26.29	-9.78	0.41	-28.7	9.1
Maximum						
0.5 hour	1.679	1.661	1.05	0.30	-22.0	24.1
1.0 hour	1.856	1.780	4.24	0.45	-13.7	22.2
2.0 hour	2.096	2.012	4.15	0.57	-11.3	19.6
6.0 hour	2.265	2.479	-8.62	0.64	- 22.8	5.6

Chromameter results for the 16 -hour duration of application in Period II.

	Least Squares Means		Observed Diff.	90% Conf. Interval (%)		
Reading	Test	Reference	(%)*	Power	Lower	Upper
18 hour	1.723	1.571	9.66	0.28	-14.0	33.3

* None of the differences was detected as statistically significant by ANOVA (a = 0.05).

Comments: It can be seen from these results that although the means of the chromameter readings at the various time points are reasonably similar, the variability of the data is so great that the 90% confidence intervals are consistently greater that 20%. These results are not unexpected, given reports of difficulty by other investigators in achieving consistent results with the chromameter.

B. Visual evaluation

The following tables give the numbers of patients who exhibited the noted visual blanching scores by duration of application and by hour of assessment after drug removal: Those tables which do not have columns for scores of 2 or 3 indicate that no patients exhibited vasoconstriction scores of 2 or 3 during the time period being evaluated. Also, it should be noted that there were two separate scoring periods (1 and 2).

STUDY 9316902C: RESULTS OF VISUAL SCORING IN PERIOD 1

FREQUENCY OF SCORES FOR EACH DURATION OF APPLICATION AT EACH ASSESSMENT HOUR READ

---------- DURATION=0.5 HOUR=6 ----------

TABLE OF TRTMNT BY SCORE

TRTMNT	SCORE		
Frequency	0	1	Total
REF	34	2	36
TEST	35	1	36
VEHCL	63	9	72
Total	132	12	144

---------- DURATION=0.5 HOUR=6 ----------

TRTMNT	N Obs	Mean
REF	36	0.06
TEST	36	0.03
VEHCL	72	0.13

FREQUENCY OF SCORES FOR EACH DURATION OF APPLICATION AT EACH ASSESSMENT HOUR READ

---------- DURATION=0.5 HOUR=8 ----------

TABLE OF TRTMNT BY SCORE

TRTMNT / Frequency	0	1	2	Total
REF	28	8	0	36
TEST	24	11	1	36
VEHCL	67	5	0	72
Total	119	24	1	144

---------- DURATION=0.5 HOUR=8 ----------

TRTMNT	N Obs	Mean
REF	36	0.22
TEST	36	0.36
VEHCL	72	0.07

STUDY 9316902C: RESULTS OF VISUAL SCORING IN PERIOD 1

FREQUENCY OF SCORES FOR EACH DURATION OF APPLICATION AT EACH ASSESSMENT HOUR READ

DURATION=0.5 HOUR=10

TABLE OF TRTMNT BY SCORE

TRTMNT / SCORE	0	1	2	Total
Frequency				
REF	26	10	0	36
TEST	22	12	2	36
VEHCL	65	7	0	72
Total	113	29	2	144

DURATION=0.5 HOUR=10

TRTMNT	N Obs	Mean
REF	36	0.28
TEST	36	0.44
VEHCL	72	0.10

STUDY 9316902C: RESULTS OF VISUAL SCORING IN PERIOD 1

FREQUENCY OF SCORES FOR EACH DURATION OF APPLICATION AT EACH ASSESSMENT HOUR READ

---------- DURATION=0.5 HOUR=12 ----------

TABLE OF TRTMNT BY SCORE

TRTMNT	SCORE			
Frequency	0	1	2	Total
REF	27	9	0	36
TEST	23	11	2	36
VEHCL	68	4	0	72
Total	118	24	2	144

---------- DURATION=0.5 HOUR=12 ----------

TRTMNT	N Obs	Mean
REF	36	0.25
TEST	36	0.42
VEHCL	72	0.06

STUDY 9316902C: RESULTS OF VISUAL SCORING IN PERIOD 1

FREQUENCY OF SCORES FOR EACH DURATION OF APPLICATION AT EACH ASSESSMENT HOUR READ

DURATION=0.5 HOUR=15

TABLE OF TRTMNT BY SCORE

TRTMNT / SCORE	0	1	2	Total
Frequency				
REF	22	14	0	36
TEST	18	17	1	36
VEHCL	67	4	0	71
Total	107	35	1	143

Frequency Missing = 1

DURATION=0.5 HOUR=15

TRTMNT	N Obs	Mean
REF	36	0.39
TEST	36	0.53
VEHCL	72	0.06

STUDY 9316902C: RESULTS OF VISUAL SCORING IN PERIOD 1

FREQUENCY OF SCORES FOR EACH DURATION OF APPLICATION AT EACH ASSESSMENT HOUR READ

---------- DURATION=0.5 HOUR=18 ----------

TABLE OF TRTMNT BY SCORE

TRTMNT	SCORE			
Frequency	0	1	2	Total
REF	25	11	0	36
TEST	22	13	1	36
VEHCL	71	1	0	72
Total	118	25	1	144

---------- DURATION=0.5 HOUR=18 ----------

TRTMNT	N Obs	Mean
REF	36	0.31
TEST	36	0.42
VEHCL	72	0.01

STUDY 9316902C: RESULTS OF VISUAL SCORING IN PERIOD 1

FREQUENCY OF SCORES FOR EACH DURATION OF APPLICATION AT EACH ASSESSMENT HOUR READ

---------- DURATION=0.5 HOUR=24 ----------

TABLE OF TRTMNT BY SCORE

TRTMNT	SCORE				
Frequency	0	1	2	3	Total
REF	29	7	0	0	36
TEST	27	7	1	1	36
VEHCL	71	1	0	0	72
Total	127	15	1	1	144

---------- DURATION=0.5 HOUR=24 ----------

TRTMNT	N Obs	Mean
REF	36	0.19
TEST	36	0.33
VEHCL	72	0.01

STUDY 9316902C: RESULTS OF VISUAL SCORING IN PERIOD 1

FREQUENCY OF SCORES FOR EACH DURATION OF APPLICATION AT EACH ASSESSMENT HOUR READ

---------- DURATION=1 HOUR=6 ----------

TABLE OF TRTMNT BY SCORE

TRTMNT	SCORE		
Frequency	0	1	Total
REF	30	6	36
TEST	29	7	36
VEHCL	63	9	72
Total	122	22	144

---------- DURATION=1 HOUR=6 ----------

TRTMNT	N Obs	Mean
REF	36	0.17
TEST	36	0.19
VEHCL	72	0.13

STUDY 9316902C: RESULTS OF VISUAL SCORING IN PERIOD 1

FREQUENCY OF SCORES FOR EACH DURATION OF APPLICATION AT EACH ASSESSMENT HOUR READ

DURATION=1 HOUR=8

TABLE OF TRTMNT BY SCORE

TRTMNT	SCORE			
Frequency	0	1	2	Total
REF	20	12	4	36
TEST	19	12	5	36
VEHCL	67	5	0	72
Total	106	29	9	144

DURATION=1 HOUR=8

TRTMNT	N Obs	Mean
REF	36	0.56
TEST	36	0.61
VEHCL	72	0.07

STUDY 9316902C: RESULTS OF VISUAL SCORING IN PERIOD 1

FREQUENCY OF SCORES FOR EACH DURATION OF APPLICATION AT EACH ASSESSMENT HOUR READ

DURATION=1 HOUR=10

TABLE OF TRTMNT BY SCORE

TRTMNT / Frequency	SCORE 0	1	2	Total
REF	15	13	8	36
TEST	15	13	8	36
VEHCL	65	7	0	72
Total	95	33	16	144

DURATION=1 HOUR=10

TRTMNT	N Obs	Mean
REF	36	0.81
TEST	36	0.81
VEHCL	72	0.10

STUDY 9316902C: RESULTS OF VISUAL SCORING IN PERIOD 1

FREQUENCY OF SCORES FOR EACH DURATION OF APPLICATION AT EACH ASSESSMENT HOUR READ

---------- DURATION=1 HOUR=12 ----------

TABLE OF TRTMNT BY SCORE

TRTMNT SCORE

Frequency	0	1	2	3	Total
REF	14	16	6	0	36
TEST	14	15	6	1	36
VEHCL	68	4	0	0	72
Total	96	35	12	1	144

---------- DURATION=1 HOUR=12 ----------

TRTMNT	N Obs	Mean
REF	36	0.78
TEST	36	0.83
VEHCL	72	0.06

STUDY 9316902C: RESULTS OF VISUAL SCORING IN PERIOD 1

FREQUENCY OF SCORES FOR EACH DURATION OF APPLICATION AT EACH ASSESSMENT HOUR READ

---------- DURATION=1 HOUR=15 ----------

TABLE OF TRTMNT BY SCORE

TRTMNT SCORE

Frequency	0	1	2	3	Total
REF	12	16	7	1	36
TEST	11	15	9	1	36
VEHCL	67	4	0	0	71
Total	90	35	16	2	143

Frequency Missing = 1

---------- DURATION=1 HOUR=15 ----------

TRTMNT	N Obs	Mean
REF	36	0.92
TEST	36	1.00
VEHCL	72	0.06

STUDY 9316902C: RESULTS OF VISUAL SCORING IN PERIOD 1

FREQUENCY OF SCORES FOR EACH DURATION OF APPLICATION AT EACH ASSESSMENT HOUR READ

---------- DURATION=1 HOUR=18 ----------

TABLE OF TRTMNT BY SCORE

TRTMNT	SCORE				
Frequency	0	1	2	3	Total
REF	16	11	8	1	36
TEST	16	13	7	0	36
VEHCL	71	1	0	0	72
Total	103	25	15	1	144

---------- DURATION=1 HOUR=18 ----------

TRTMNT	N Obs	Mean
REF	36	0.83
TEST	36	0.75
VEHCL	72	0.01

STUDY 9316902C: RESULTS OF VISUAL SCORING IN PERIOD 1

FREQUENCY OF SCORES FOR EACH DURATION OF APPLICATION AT EACH ASSESSMENT HOUR READ

---------- DURATION=1 HOUR=24 ----------

TABLE OF TRTMNT BY SCORE

TRTMNT	SCORE			
Frequency	0	1	2	Total
REF	20	12	4	36
TEST	22	10	4	36
VEHCL	71	1	0	72
Total	113	23	8	144

---------- DURATION=1 HOUR=24 ----------

TRTMNT	N Obs	Mean
REF	36	0.56
TEST	36	0.50
VEHCL	72	0.01

STUDY 9316902C: RESULTS OF VISUAL SCORING IN PERIOD 1

FREQUENCY OF SCORES FOR EACH DURATION OF APPLICATION AT EACH ASSESSMENT HOUR READ

---------- DURATION=2 HOUR=6 ----------

TABLE OF TRTMNT BY SCORE

TRTMNT	SCORE			
Frequency	0	1	2	Total
REF	31	5	0	36
TEST	31	4	1	36
VEHCL	63	9	0	72
Total	125	18	1	144

---------- DURATION=2 HOUR=6 ----------

TRTMNT	N Obs	Mean
REF	36	0.14
TEST	36	0.17
VEHCL	72	0.13

STUDY 9316902C: RESULTS OF VISUAL SCORING IN PERIOD 1

FREQUENCY OF SCORES FOR EACH DURATION OF APPLICATION AT EACH ASSESSMENT HOUR READ

---------- DURATION=2 HOUR=8 ----------

TABLE OF TRTMNT BY SCORE

TRTMNT SCORE

Frequency	0	1	2	3	Total
REF	14	14	7	1	36
TEST	15	15	6	0	36
VEHCL	67	5	0	0	72
Total	96	34	13	1	144

---------- DURATION=2 HOUR=8 ----------

TRTMNT	N Obs	Mean
REF	36	0.86
TEST	36	0.75
VEHCL	72	0.07

STUDY 9316902C: RESULTS OF VISUAL SCORING IN PERIOD 1

FREQUENCY OF SCORES FOR EACH DURATION OF APPLICATION AT EACH ASSESSMENT HOUR READ

---------- DURATION=2 HOUR=10 ----------

TABLE OF TRTMNT BY SCORE

TRTMNT SCORE

Frequency	0	1	2	3	Total
REF	8	14	13	1	36
TEST	10	14	11	1	36
VEHCL	65	7	0	0	72
Total	83	35	24	2	144

---------- DURATION=2 HOUR=10 ----------

TRTMNT	N Obs	Mean
REF	36	1.19
TEST	36	1.08
VEHCL	72	0.10

STUDY 9316902C: RESULTS OF VISUAL SCORING IN PERIOD 1

FREQUENCY OF SCORES FOR EACH DURATION OF APPLICATION AT EACH ASSESSMENT HOUR READ

---------- DURATION=2 HOUR=12 ----------

TABLE OF TRTMNT BY SCORE

TRTMNT	SCORE				
Frequency	0	1	2	3	Total
REF	13	11	10	2	36
TEST	11	13	9	3	36
VEHCL	68	4	0	0	72
Total	92	28	19	5	144

---------- DURATION=2 HOUR=12 ----------

TRTMNT	N Obs	Mean
REF	36	1.03
TEST	36	1.11
VEHCL	72	0.06

STUDY 9316902C: RESULTS OF VISUAL SCORING IN PERIOD 1

FREQUENCY OF SCORES FOR EACH DURATION OF APPLICATION AT EACH ASSESSMENT HOUR READ

---------- DURATION=2 HOUR=15 ----------

TABLE OF TRTMNT BY SCORE

TRTMNT SCORE

Frequency	0	1	2	3	Total
REF	11	8	13	4	36
TEST	9	8	16	3	36
VEHCL	67	4	0	0	71
Total	87	20	29	7	143

Frequency Missing = 1

---------- DURATION=2 HOUR=15 ----------

TRTMNT	N Obs	Mean
REF	36	1.28
TEST	36	1.36
VEHCL	72	0.06

STUDY 9316902C: RESULTS OF VISUAL SCORING IN PERIOD 1

FREQUENCY OF SCORES FOR EACH DURATION OF APPLICATION AT EACH ASSESSMENT HOUR READ

---------- DURATION=2 HOUR=18 ----------

TABLE OF TRTMNT BY SCORE

TRTMNT	SCORE				
Frequency	0	1	2	3	Total
REF	11	11	9	5	36
TEST	11	12	11	2	36
VEHCL	71	1	0	0	72
Total	93	24	20	7	144

---------- DURATION=2 HOUR=18 ----------

TRTMNT	N Obs	Mean
REF	36	1.22
TEST	36	1.11
VEHCL	72	0.01

STUDY 9316902C: RESULTS OF VISUAL SCORING IN PERIOD 1

FREQUENCY OF SCORES FOR EACH DURATION OF APPLICATION AT EACH ASSESSMENT HOUR READ

---------- DURATION=2 HOUR=24 ----------

TABLE OF TRTMNT BY SCORE

TRTMNT / SCORE	0	1	2	Total
Frequency				
REF	18	12	6	36
TEST	20	10	6	36
VEHCL	71	1	0	72
Total	109	23	12	144

---------- DURATION=2 HOUR=24 ----------

TRTMNT	N Obs	Mean
REF	36	0.67
TEST	36	0.61
VEHCL	72	0.01

STUDY 9316902C: RESULTS OF VISUAL SCORING IN PERIOD 1

FREQUENCY OF SCORES FOR EACH DURATION OF APPLICATION AT EACH ASSESSMENT HOUR READ

---------- DURATION=6 HOUR=6 ----------

TABLE OF TRTMNT BY SCORE

TRTMNT SCORE

Frequency	0	1	2	Total
REF	22	12	2	36
TEST	16	17	3	36
VEHCL	63	9	0	72
Total	101	38	5	144

---------- DURATION=6 HOUR=6 ----------

TRTMNT	N Obs	Mean
REF	36	0.44
TEST	36	0.64
VEHCL	72	0.13

STUDY 9316902C: RESULTS OF VISUAL SCORING IN PERIOD 1

FREQUENCY OF SCORES FOR EACH DURATION OF APPLICATION AT EACH ASSESSMENT HOUR READ

DURATION=6 HOUR=8

TABLE OF TRTMNT BY SCORE

TRTMNT / SCORE	0	1	2	3	Total
Frequency					
REF	13	13	8	2	36
TEST	10	17	7	2	36
VEHCL	67	5	0	0	72
Total	90	35	15	4	144

DURATION=6 HOUR=8

TRTMNT	N Obs	Mean
REF	36	0.97
TEST	36	1.03
VEHCL	72	0.07

STUDY 9316902C: RESULTS OF VISUAL SCORING IN PERIOD 1

FREQUENCY OF SCORES FOR EACH DURATION OF APPLICATION AT EACH ASSESSMENT HOUR READ

DURATION=6 HOUR=10

TABLE OF TRTMNT BY SCORE

TRTMNT / Frequency	0	1	2	3	Total
REF	8	13	13	2	36
TEST	9	9	15	3	36
VEHCL	65	7	0	0	72
Total	82	29	28	5	144

DURATION=6 HOUR=10

TRTMNT	N Obs	Mean
REF	36	1.25
TEST	36	1.33
VEHCL	72	0.10

STUDY 9316902C: RESULTS OF VISUAL SCORING IN PERIOD 1

FREQUENCY OF SCORES FOR EACH DURATION OF APPLICATION AT EACH ASSESSMENT HOUR READ

DURATION=6 HOUR=12

TABLE OF TRTMNT BY SCORE

TRTMNT / Frequency	0	1	2	3	Total
REF	6	12	15	3	36
TEST	7	10	13	6	36
VEHCL	68	4	0	0	72
Total	81	26	28	9	144

DURATION=6 HOUR=12

TRTMNT	N Obs	Mean
REF	36	1.42
TEST	36	1.50
VEHCL	72	0.06

STUDY 9316902C: RESULTS OF VISUAL SCORING IN PERIOD 1

FREQUENCY OF SCORES FOR EACH DURATION OF APPLICATION AT EACH ASSESSMENT HOUR READ

---------- DURATION=6 HOUR=15 ----------

TABLE OF TRTMNT BY SCORE

TRTMNT SCORE

Frequency	0	1	2	3	Total
REF	4	9	16	7	36
TEST	4	9	13	10	36
VEHCL	67	4	0	0	71
Total	75	22	29	17	143

Frequency Missing = 1

---------- DURATION=6 HOUR=15 ----------

TRTMNT	N Obs	Mean
REF	36	1.72
TEST	36	1.81
VEHCL	72	0.06

STUDY 9316902C: RESULTS OF VISUAL SCORING IN PERIOD 1

FREQUENCY OF SCORES FOR EACH DURATION OF APPLICATION AT EACH ASSESSMENT HOUR READ

---------- DURATION=6 HOUR=18 ----------

TABLE OF TRTMNT BY SCORE

TRTMNT / SCORE	0	1	2	3	Total
Frequency					
REF	9	7	11	9	36
TEST	6	6	22	2	36
VEHCL	71	1	0	0	72
Total	86	14	33	11	144

---------- DURATION=6 HOUR=18 ----------

TRTMNT	N Obs	Mean
REF	36	1.56
TEST	36	1.56
VEHCL	72	0.01

STUDY 9316902C: RESULTS OF VISUAL SCORING IN PERIOD 1

FREQUENCY OF SCORES FOR EACH DURATION OF APPLICATION AT EACH ASSESSMENT HOUR READ

DURATION=6 HOUR=24

TABLE OF TRTMNT BY SCORE

TRTMNT SCORE

Frequency	0	1	2	3	Total
REF	13	12	11	0	36
TEST	6	18	11	1	36
VEHCL	71	1	0	0	72
Total	90	31	22	1	144

DURATION=6 HOUR=24

TRTMNT	N Obs	Mean
REF	36	0.94
TEST	36	1.19
VEHCL	72	0.01

STUDY 9316902C: RESULTS OF VISUAL SCORING IN PERIOD 1

FREQUENCY OF SCORES FOR EACH DURATION OF APPLICATION AT EACH ASSESSMENT HOUR READ

---------- DURATION=16 HOUR=18 ----------

TABLE OF TRTMNT BY SCORE

TRTMNT	SCORE				
Frequency	0	1	2	3	Total
REF	1	11	17	7	36
TEST	5	9	12	10	36
VEHCL	71	1	0	0	72
Total	77	21	29	17	144

---------- DURATION=16 HOUR=18 ----------

TRTMNT	N Obs	Mean
REF	36	1.83
TEST	36	1.75
VEHCL	72	0.01

STUDY 9316902C: RESULTS OF VISUAL SCORING IN PERIOD 1

FREQUENCY OF SCORES FOR EACH DURATION OF APPLICATION AT EACH ASSESSMENT HOUR READ

---------- DURATION=16 HOUR=24 ----------

TABLE OF TRTMNT BY SCORE

TRTMNT	SCORE				
Frequency	0	1	2	3	Total
REF	11	14	10	1	36
TEST	8	15	12	1	36
VEHCL	71	1	0	0	72
Total	90	30	22	2	144

---------- DURATION=16 HOUR=24 ----------

TRTMNT	N Obs	Mean
REF	36	1.03
TEST	36	1.17
VEHCL	72	0.01

STUDY NO. 9316902C

VISUAL SCORING IN

PERIOD II

STUDY 9316902C: RESULTS OF VISUAL SCORING IN PERIOD 2

FREQUENCY OF SCORES FOR EACH DURATION OF APPLICATION AT EACH ASSESSMENT HOUR READ

---------- DURATION=0.5 HOUR=6 ----------

TABLE OF TRTMNT BY SCORE

TRTMNT	SCORE			
Frequency	0	1	2	Total
REF	32	8	0	40
TEST	31	8	1	40
VEHCL	45	26	9	80
Total	108	42	10	160

---------- DURATION=0.5 HOUR=6 ----------

TRTMNT	N Obs	Mean
REF	40	0.20
TEST	40	0.25
VEHCL	80	0.55

STUDY 9316902C: RESULTS OF VISUAL SCORING IN PERIOD 2

FREQUENCY OF SCORES FOR EACH DURATION OF APPLICATION AT EACH ASSESSMENT HOUR READ

---------- DURATION=0.5 HOUR=8 ----------

TABLE OF TRTMNT BY SCORE

TRTMNT SCORE

Frequency	0	1	2	3	Total
REF	32	6	2	0	40
TEST	25	10	4	1	40
VEHCL	75	5	0	0	80
Total	132	21	6	1	160

---------- DURATION=0.5 HOUR=8 ----------

TRTMNT	N Obs	Mean
REF	40	0.25
TEST	40	0.53
VEHCL	80	0.06

STUDY 9316902C: RESULTS OF VISUAL SCORING IN PERIOD 2

FREQUENCY OF SCORES FOR EACH DURATION OF APPLICATION AT EACH ASSESSMENT HOUR READ

---------- DURATION=0.5 HOUR=10 ----------

TABLE OF TRTMNT BY SCORE

TRTMNT	SCORE				
Frequency	0	1	2	3	Total
REF	31	7	1	1	40
TEST	26	9	3	2	40
VEHCL	71	8	1	0	80
Total	128	24	5	3	160

---------- DURATION=0.5 HOUR=10 ----------

TRTMNT	N Obs	Mean
REF	40	0.30
TEST	40	0.53
VEHCL	80	0.13

STUDY 9316902C: RESULTS OF VISUAL SCORING IN PERIOD 2

FREQUENCY OF SCORES FOR EACH DURATION OF APPLICATION AT EACH ASSESSMENT HOUR READ

DURATION=0.5 HOUR=12

TABLE OF TRTMNT BY SCORE

TRTMNT	SCORE				
Frequency	0	1	2	3	Total
REF	28	9	2	1	40
TEST	21	13	4	2	40
VEHCL	74	6	0	0	80
Total	123	28	6	3	160

DURATION=0.5 HOUR=12

TRTMNT	N Obs	Mean
REF	40	0.40
TEST	40	0.68
VEHCL	80	0.08

STUDY 9316902C: RESULTS OF VISUAL SCORING IN PERIOD 2

FREQUENCY OF SCORES FOR EACH DURATION OF APPLICATION AT EACH ASSESSMENT HOUR READ

---------- DURATION=0.5 HOUR=15 ----------

TABLE OF TRTMNT BY SCORE

TRTMNT	SCORE				
Frequency	0	1	2	3	Total
REF	30	8	1	1	40
TEST	24	8	4	4	40
VEHCL	73	6	0	0	79
Total	127	22	5	5	159

Frequency Missing = 1

---------- DURATION=0.5 HOUR=15 ----------

TRTMNT	N Obs	Mean
REF	40	0.33
TEST	40	0.70
VEHCL	80	0.08

STUDY 9316902C: RESULTS OF VISUAL SCORING IN PERIOD 2

FREQUENCY OF SCORES FOR EACH DURATION OF APPLICATION AT EACH ASSESSMENT HOUR READ

---------- DURATION=0.5 HOUR=18 ----------

TABLE OF TRTMNT BY SCORE

TRTMNT	SCORE				
Frequency	0	1	2	3	Total
REF	33	5	1	1	40
TEST	27	9	1	3	40
VEHCL	77	3	0	0	80
Total	137	17	2	4	160

---------- DURATION=0.5 HOUR=18 ----------

TRTMNT	N Obs	Mean
REF	40	0.25
TEST	40	0.50
VEHCL	80	0.04

STUDY 9316902C: RESULTS OF VISUAL SCORING IN PERIOD 2

FREQUENCY OF SCORES FOR EACH DURATION OF APPLICATION AT EACH ASSESSMENT HOUR READ

---------- DURATION=0.5 HOUR=24 ----------

TABLE OF TRTMNT BY SCORE

TRTMNT	SCORE				
Frequency	0	1	2	3	Total
REF	33	5	1	1	40
TEST	25	10	5	0	40
VEHCL	76	4	0	0	80
Total	134	19	6	1	160

---------- DURATION=0.5 HOUR=24 ----------

TRTMNT	N Obs	Mean
REF	40	0.25
TEST	40	0.50
VEHCL	80	0.05

STUDY 9316902C: RESULTS OF VISUAL SCORING IN PERIOD 2

FREQUENCY OF SCORES FOR EACH DURATION OF APPLICATION AT EACH ASSESSMENT HOUR READ

---------- DURATION=1 HOUR=6 ----------

TABLE OF TRTMNT BY SCORE

TRTMNT SCORE

Frequency	0	1	2	Total
REF	28	8	4	40
TEST	29	8	3	40
VEHCL	45	26	9	80
Total	102	42	16	160

---------- DURATION=1 HOUR=6 ----------

TRTMNT	N Obs	Mean
REF	40	0.40
TEST	40	0.35
VEHCL	80	0.55

STUDY 9316902C: RESULTS OF VISUAL SCORING IN PERIOD 2

FREQUENCY OF SCORES FOR EACH DURATION OF APPLICATION AT EACH ASSESSMENT HOUR READ

DURATION=1 HOUR=8

TABLE OF TRTMNT BY SCORE

TRTMNT / SCORE	0	1	2	3	Total
Frequency					
REF	21	13	5	1	40
TEST	22	11	6	1	40
VEHCL	75	5	0	0	80
Total	118	29	11	2	160

DURATION=1 HOUR=8

TRTMNT	N Obs	Mean
REF	40	0.65
TEST	40	0.65
VEHCL	80	0.06

STUDY 9316902C: RESULTS OF VISUAL SCORING IN PERIOD 2

FREQUENCY OF SCORES FOR EACH DURATION OF APPLICATION AT EACH ASSESSMENT HOUR READ

---------- DURATION=1 HOUR=10 ----------

TABLE OF TRTMNT BY SCORE

TRTMNT SCORE

Frequency	0	1	2	3	Total
REF	21	11	5	3	40
TEST	16	16	4	4	40
VEHCL	71	8	1	0	80
Total	108	35	10	7	160

---------- DURATION=1 HOUR=10 ----------

TRTMNT	N Obs	Mean
REF	40	0.75
TEST	40	0.90
VEHCL	80	0.13

STUDY 9316902C: RESULTS OF VISUAL SCORING IN PERIOD 2

FREQUENCY OF SCORES FOR EACH DURATION OF APPLICATION AT EACH ASSESSMENT HOUR READ

---------- DURATION=1 HOUR=12 ----------

TABLE OF TRTMNT BY SCORE

TRTMNT / SCORE	0	1	2	3	Total
Frequency					
REF	20	8	8	4	40
TEST	17	13	6	4	40
VEHCL	74	6	0	0	80
Total	111	27	14	8	160

---------- DURATION=1 HOUR=12 ----------

TRTMNT	N Obs	Mean
REF	40	0.90
TEST	40	0.93
VEHCL	80	0.08

STUDY 9316902C: RESULTS OF VISUAL SCORING IN PERIOD 2

FREQUENCY OF SCORES FOR EACH DURATION OF APPLICATION AT EACH ASSESSMENT HOUR READ

DURATION=1 HOUR=15

TABLE OF TRTMNT BY SCORE

TRTMNT / Frequency	0	1	2	3	Total
REF	17	10	11	2	40
TEST	13	13	11	3	40
VEHCL	73	6	0	0	79
Total	103	29	22	5	159

Frequency Missing = 1

DURATION=1 HOUR=15

TRTMNT	N Obs	Mean
REF	40	0.95
TEST	40	1.10
VEHCL	80	0.08

STUDY 9316902C: RESULTS OF VISUAL SCORING IN PERIOD 2

FREQUENCY OF SCORES FOR EACH DURATION OF APPLICATION AT EACH ASSESSMENT HOUR READ

---------- DURATION=1 HOUR=18 ----------

TABLE OF TRTMNT BY SCORE

TRTMNT	SCORE				
Frequency	0	1	2	3	Total
REF	18	12	8	2	40
TEST	13	17	8	2	40
VEHCL	77	3	0	0	80
Total	108	32	16	4	160

---------- DURATION=1 HOUR=18 ----------

TRTMNT	N Obs	Mean
REF	40	0.85
TEST	40	0.98
VEHCL	80	0.04

STUDY 9316902C: RESULTS OF VISUAL SCORING IN PERIOD 2

FREQUENCY OF SCORES FOR EACH DURATION OF APPLICATION AT EACH ASSESSMENT HOUR READ

DURATION=1 HOUR=24

TABLE OF TRTMNT BY SCORE

TRTMNT SCORE

Frequency	0	1	2	Total
REF	21	16	3	40
TEST	22	11	7	40
VEHCL	76	4	0	80
Total	119	31	10	160

DURATION=1 HOUR=24

TRTMNT	N Obs	Mean
REF	40	0.55
TEST	40	0.63
VEHCL	80	0.05

STUDY 9316902C: RESULTS OF VISUAL SCORING IN PERIOD 2

FREQUENCY OF SCORES FOR EACH DURATION OF APPLICATION AT EACH ASSESSMENT HOUR READ

DURATION=2 HOUR=6

TABLE OF TRTMNT BY SCORE

TRTMNT SCORE

Frequency	0	1	2	Total
REF	24	13	3	40
TEST	24	13	3	40
VEHCL	45	26	9	80
Total	93	52	15	160

DURATION=2 HOUR=6

TRTMNT	N Obs	Mean
REF	40	0.48
TEST	40	0.48
VEHCL	80	0.55

STUDY 9316902C: RESULTS OF VISUAL SCORING IN PERIOD 2

FREQUENCY OF SCORES FOR EACH DURATION OF APPLICATION AT EACH ASSESSMENT HOUR READ

DURATION=2 HOUR=8

TABLE OF TRTMNT BY SCORE

TRTMNT SCORE

Frequency	0	1	2	3	Total
REF	13	16	9	2	40
TEST	14	15	9	2	40
VEHCL	75	5	0	0	80
Total	102	36	18	4	160

DURATION=2 HOUR=8

TRTMNT	N Obs	Mean
REF	40	1.00
TEST	40	0.98
VEHCL	80	0.06

STUDY 9316902C: RESULTS OF VISUAL SCORING IN PERIOD 2

FREQUENCY OF SCORES FOR EACH DURATION OF APPLICATION AT EACH ASSESSMENT HOUR READ

DURATION=2 HOUR=10

TABLE OF TRTMNT BY SCORE

TRTMNT / Frequency	SCORE 0	1	2	3	Total
REF	10	12	12	6	40
TEST	10	16	7	7	40
VEHCL	71	8	1	0	80
Total	91	36	20	13	160

DURATION=2 HOUR=10

TRTMNT	N Obs	Mean
REF	40	1.35
TEST	40	1.28
VEHCL	80	0.13

STUDY 9316902C: RESULTS OF VISUAL SCORING IN PERIOD 2

FREQUENCY OF SCORES FOR EACH DURATION OF APPLICATION AT EACH ASSESSMENT HOUR READ

DURATION=2 HOUR=12

TABLE OF TRTMNT BY SCORE

TRTMNT / SCORE	0	1	2	3	Total
Frequency					
REF	6	14	14	6	40
TEST	8	15	10	7	40
VEHCL	74	6	0	0	80
Total	88	35	24	13	160

DURATION=2 HOUR=12

TRTMNT	N Obs	Mean
REF	40	1.50
TEST	40	1.40
VEHCL	80	0.08

STUDY 9316902C: RESULTS OF VISUAL SCORING IN PERIOD 2

FREQUENCY OF SCORES FOR EACH DURATION OF APPLICATION AT EACH ASSESSMENT HOUR READ

DURATION=2 HOUR=15

TABLE OF TRTMNT BY SCORE

TRTMNT	SCORE				
Frequency	0	1	2	3	Total
REF	6	12	15	7	40
TEST	7	9	17	7	40
VEHCL	73	6	0	0	79
Total	86	27	32	14	159

Frequency Missing = 1

DURATION=2 HOUR=15

TRTMNT	N Obs	Mean
REF	40	1.58
TEST	40	1.60
VEHCL	80	0.08

STUDY 9316902C: RESULTS OF VISUAL SCORING IN PERIOD 2

FREQUENCY OF SCORES FOR EACH DURATION OF APPLICATION AT EACH ASSESSMENT HOUR READ

DURATION=2 HOUR=18

TABLE OF TRTMNT BY SCORE

TRTMNT	SCORE				
Frequency	0	1	2	3	Total
REF	9	12	13	6	40
TEST	10	12	9	9	40
VEHCL	77	3	0	0	80
Total	96	27	22	15	160

DURATION=2 HOUR=18

TRTMNT	N Obs	Mean
REF	40	1.40
TEST	40	1.43
VEHCL	80	0.04

STUDY 9316902C: RESULTS OF VISUAL SCORING IN PERIOD 2

FREQUENCY OF SCORES FOR EACH DURATION OF APPLICATION AT EACH ASSESSMENT HOUR READ

DURATION=2 HOUR=24

TABLE OF TRTMNT BY SCORE

TRTMNT Frequency	SCORE 0	1	2	Total
REF	14	16	10	40
TEST	21	11	8	40
VEHCL	76	4	0	80
Total	111	31	18	160

DURATION=2 HOUR=24

TRTMNT	N Obs	Mean
REF	40	0.90
TEST	40	0.68
VEHCL	80	0.05

STUDY 9316902C: RESULTS OF VISUAL SCORING IN PERIOD 2

FREQUENCY OF SCORES FOR EACH DURATION OF APPLICATION AT EACH ASSESSMENT HOUR READ

DURATION=6 HOUR=6

TABLE OF TRTMNT BY SCORE

TRTMNT / SCORE	0	1	2	3	Total
Frequency					
REF	7	17	15	1	40
TEST	10	18	12	0	40
VEHCL	45	26	9	0	80
Total	62	61	36	1	160

DURATION=6 HOUR=6

TRTMNT	N Obs	Mean
REF	40	1.25
TEST	40	1.05
VEHCL	80	0.55

STUDY 9316902C: RESULTS OF VISUAL SCORING IN PERIOD 2

FREQUENCY OF SCORES FOR EACH DURATION OF APPLICATION AT EACH ASSESSMENT HOUR READ

---------- DURATION=6 HOUR=8 ----------

TABLE OF TRTMNT BY SCORE

TRTMNT	SCORE				
Frequency	0	1	2	3	Total
REF	5	15	14	6	40
TEST	9	16	12	3	40
VEHCL	75	5	0	0	80
Total	89	36	26	9	160

---------- DURATION=6 HOUR=8 ----------

TRTMNT	N Obs	Mean
REF	40	1.53
TEST	40	1.23
VEHCL	80	0.06

STUDY 9316902C: RESULTS OF VISUAL SCORING IN PERIOD 2

FREQUENCY OF SCORES FOR EACH DURATION OF APPLICATION AT EACH ASSESSMENT HOUR READ

DURATION=6 HOUR=10

TABLE OF TRTMNT BY SCORE

TRTMNT / SCORE	0	1	2	3	Total
Frequency					
REF	3	12	12	13	40
TEST	6	13	12	9	40
VEHCL	71	8	1	0	80
Total	80	33	25	22	160

DURATION=6 HOUR=10

TRTMNT	N Obs	Mean
REF	40	1.88
TEST	40	1.60
VEHCL	80	0.13

STUDY 9316902C: RESULTS OF VISUAL SCORING IN PERIOD 2

FREQUENCY OF SCORES FOR EACH DURATION OF APPLICATION AT EACH ASSESSMENT HOUR READ

---------- DURATION=6 HOUR=12 ----------

TABLE OF TRTMNT BY SCORE

TRTMNT	SCORE				
Frequency	0	1	2	3	Total
REF	1	7	19	13	40
TEST	2	10	16	12	40
VEHCL	74	6	0	0	80
Total	77	23	35	25	160

---------- DURATION=6 HOUR=12 ----------

TRTMNT	N Obs	Mean
REF	40	2.10
TEST	40	1.95
VEHCL	80	0.08

STUDY 9316902C: RESULTS OF VISUAL SCORING IN PERIOD 2

FREQUENCY OF SCORES FOR EACH DURATION OF APPLICATION AT EACH ASSESSMENT HOUR READ

DURATION=6 HOUR=15

TABLE OF TRTMNT BY SCORE

TRTMNT SCORE

Frequency	0	1	2	3	Total
REF	0	9	17	14	40
TEST	1	9	14	16	40
VEHCL	73	6	0	0	79
Total	74	24	31	30	159

Frequency Missing = 1

DURATION=6 HOUR=15

TRTMNT	N Obs	Mean
REF	40	2.13
TEST	40	2.13
VEHCL	80	0.08

STUDY 9316902C: RESULTS OF VISUAL SCORING IN PERIOD 2

FREQUENCY OF SCORES FOR EACH DURATION OF APPLICATION AT EACH ASSESSMENT HOUR READ

DURATION=6 HOUR=18

TABLE OF TRTMNT BY SCORE

TRTMNT	SCORE				
Frequency	0	1	2	3	Total
REF	2	15	11	12	40
TEST	4	12	12	12	40
VEHCL	77	3	0	0	80
Total	83	30	23	24	160

DURATION=6 HOUR=18

TRTMNT	N Obs	Mean
REF	40	1.83
TEST	40	1.80
VEHCL	80	0.04

STUDY 9316902C: RESULTS OF VISUAL SCORING IN PERIOD 2

FREQUENCY OF SCORES FOR EACH DURATION OF APPLICATION AT EACH ASSESSMENT HOUR READ

---------- DURATION=6 HOUR=24 ----------

TABLE OF TRTMNT BY SCORE

TRTMNT	SCORE			
Frequency	0	1	2	Total
REF	13	15	12	40
TEST	12	20	8	40
VEHCL	76	4	0	80
Total	101	39	20	160

---------- DURATION=6 HOUR=24 ----------

TRTMNT	N Obs	Mean
REF	40	0.98
TEST	40	0.90
VEHCL	80	0.05

STUDY 9316902C: RESULTS OF VISUAL SCORING IN PERIOD 2

FREQUENCY OF SCORES FOR EACH DURATION OF APPLICATION AT EACH ASSESSMENT HOUR READ

---------- DURATION=16 HOUR=18 ----------

TABLE OF TRTMNT BY SCORE

TRTMNT SCORE

Frequency	0	1	2	3	Total
REF	2	14	9	15	40
TEST	5	4	17	14	40
VEHCL	77	3	0	0	80
Total	84	21	26	29	160

---------- DURATION=16 HOUR=18 ----------

TRTMNT	N Obs	Mean
REF	40	1.93
TEST	40	2.00
VEHCL	80	0.04

STUDY 9316902C: RESULTS OF VISUAL SCORING IN PERIOD 2

FREQUENCY OF SCORES FOR EACH DURATION OF APPLICATION AT EACH ASSESSMENT HOUR READ

---------- DURATION=16 HOUR=24 ----------

TABLE OF TRTMNT BY SCORE

TRTMNT / SCORE	0	1	2	3	Total
Frequency					
REF	12	13	14	1	40
TEST	7	19	11	3	40
VEHCL	76	4	0	0	80
Total	95	36	25	4	160

---------- DURATION=16 HOUR=24 ----------

TRTMNT	N Obs	Mean
REF	40	1.10
TEST	40	1.25
VEHCL	80	0.05

Comment: Little visual vasoconstriction was seen for the 0.5 hour duration of application. However, betamethasone dipropionate cream 0.05% and Diprosone Cream 0.05% are comparable in their vasoconstrictor activity. If the totals of the mean scores for all evaluations are taken by time period, the following is seen:

Scoring Period #1

Test Product	Mean Total
Clay - Park betamethasone dipropionate	23.39
Diprosone Cream	23.88
Clay- Park Vehicle	1.78

Scoring Period #2

Test Product	Mean Total
Clay-Park betamethasome Dipropionate	30.99
Diprosone Cream	29.97
Clay -Park Vehicle	4.05

Thus, the Clay-Park product achieved 106.3% of the mean total vasoconstriction of Diprosone during scoring period #1, and 103.4% of this total during scoring period #2. Both products were superior to the Clay-park vehicle.

Conclusions and Recommendation: This ANDA may be approved on the basis of bioequivalence in that the vasoconstrictor activity of the test and reference products are not significantly different. The chromameter results suggest comparability, but the variance in the data causes wide confidence intervals in the statistical analysis.

Because of reported difficulties in achieving consistent chromameter results, the July 1, 1992 Guidance under which this study was performed has been superseded by another guidance dated December 1, 1994. The new guidance recommends a pilot vasoconstrictor study be done in order to validate chromameter readings in a selected group of "good" responders. In any event, there is no reason to refuse to approve this application on the basis of inconsistent chromameter readings, since no one has been able to achieve consistent results using the old guidance.

David C. Bostwick

Jonathan Wilkin, M.D.

12/7/95

(acted for HFD-540 - 11/95)

cc: Orig. NDA 74-579
HFD-630
HFD-540/Fule
HFD-520/Bostwick
HFD-540/Wilkin